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PATENT

Case Docket No. AVANIR.000GEN
Date: September 22, 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Of	:	Katz
Appl. No.	:	07/345,084
Filed	:	April 28, 1989
Patent No.	:	4,874,794
Issued	:	October 17, 1989
For	:	INFLAMMATORY DISEASE TREATMENT
Group Art Unit	:	125
Examiner	:	Stanley J. Friedman

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on

September 22, 2000
(Date)

Mark R. Benedict, Reg. No. 44,531

TRANSMITTAL LETTER

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

ATTENTION: PATENT EXTENSION

Dear Sir:

Enclosed for filing in the above-identified patent:

(X) Application for Extension of Patent Term with Exhibits A-F (in duplicate).

(X) Certification of Duplicate Copy

(X) A check in the amount of $1120 to cover the fee is enclosed.

(X) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 11-1410. A duplicate copy of this sheet is enclosed.

(X) Return prepaid postcard.

Mark R. Benedict
Registration No.44,531
Attorney of Record

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092100

KNOBBE, MARTENS, OLSON & BEAR, LLP
620 NEWPORT CENTER DR 16TH FLOOR NEWPORT BEACH, CA 92660
(949) 760-0404 FAX (949) 760-9502

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AVANIR.000GEN PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of :		KATZ, David H.	Group Art Unit 125
Appl. No.	:	07/345,084	
Filed	:	April 28, 1989	
Patent No.	:	U. S. Patent No. 4,874,794	
Issued	:	October 17, 1989	
For	:	INFLAMMATORY DISEASE TREATMENT	
Examiner	:	FRIEDMAN, Stanley J.	

APPLICATION FOR EXTENSION OF PATENT TERM BASED ON REGULATORY REVIEW OF A NEW DRUG APPLICATION PURSUANT TO 35 U.S.C. § 156

Assistant Commissioner for Patents
Washington, D.C. 20231
Box: Patent Ext.

Dear Sir:

The Applicant, AVANIR Pharmaceuticals, of 11388 Sorrento Valley Road, San Diego, CA 92121, represents that it is the owner of record of the entire right, title and interest in and to U. S. Patent No. 4,874,794, as evidenced by the Assignments from the Inventor to LIDAK PHARMACEUTICALS recorded on April 6, 1990 under Reel/Frame: 5293/0061, and the later Assignment from LIDAK PHARMACEUTICALS to AVANIR PHARMACEUTICALS recorded on April 20, 1999 under Reel/Frame: 9901/0274. The recorded Assignments along with the two Notice of Recordation of Assignment Documents, copies of which are submitted as **Exhibit A**, refer specifically to Patent Application Serial No. 07/345,084, filed on April 28, 1989, and U.S. Patent No. 4,874,794 issued on October 17, 1989. The recorded Assignments assign the full and exclusive right, title and interest in and to the invention disclosed in Patent Application Serial No. 07/345,084, from which U.S. Patent No. 4,874,794 was granted.

Patent No : U.S. 4,874,794
Issued : October 17, 1989

AVANIR Pharmaceuticals hereby applies, pursuant to 35 U.S.C. § 156 (d) (1) and 37 C.F.R. § 1.740, for extension of the term of the above-identified U. S. Patent No. 4,874,794 issued on October 17, 1989, and based on U. S. Application Serial No. 07/345,084 filed on April 28, 1989.

U. S. Patent No. 4,874,794 results from an application filed before the date that is 6 months after the date of the enactment of the Uruguay Round Agreements Act (December 8, 1994), accordingly, its date of expiration under 35 U.S.C. § 154 (c) (1) is April 28, 2009, the greater of the 20-year term from the filing date (April 28, 1989), or 17 years from grant (October 17, 2006).

The patent term extension is requested until April 28, 2014, five years (1826 days) from the original expiration date, or such greater or lesser period as the Commissioner may deem AVANIR Pharmaceuticals to be entitled. This is the maximum permitted extension provided in 35 U.S.C. § 156. The regulatory review period (reduced by one-half of the IND period) is 2124 days, which is greater than either 14 years from the date of approval (July 25, 2014) provided in 37 C.F.R. §1.775(d)(3) or 5 years from the original expiration date (April 28, 2014) provided in 37 C.F.R. §1.775(d)(5)(i).

This application for patent term extension is based on the regulatory approval of Abreva™. The sole active ingredient in Abreva™ is 10% docosanol, a 22-carbon aliphatic alcohol.

Docosanol is produced by high-pressure hydrogenation of erucic acid, an unsaturated, 22-carbon fatty acid. Hydrogenation of erucic acid is carried out in the presence of fine-grained, slurried copper-chromite catalyst at a temperature and pressure of approximately 285° C and 300 bar, respectively. Crude *n*-docosanol is purified by multi-step, fractional distillation. Then it is processed through a post-hydrogenation plant containing a fixed-bed nickel catalyst to remove any C-22 aldehyde, which might be present in the crude material.

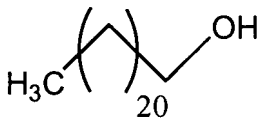
A method of using 10% docosanol, the active ingredient in Abreva™, for treating virus-induced and inflammatory diseases is claimed in U. S. Patent No. 4,874,794.

The date of the NDA approval of Abreva™ is July 25, 2000. This is the first permitted commercial marketing or use of this active ingredient as a human drug product. This application is accordingly being made within the 60-day statutory period provided in 35 U.S.C. § 156(d).

In accordance with 37 C.F.R. § 1.740, AVANIR Pharmaceuticals provides the following information:

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

AVANIR Pharmaceuticals submits herewith as **Exhibit B** to this application the prescribing information for Abreva™ as approved by the U. S. Food and Drug Administration (FDA). *n*-Docosanol, the sole active ingredient in Abreva™, is an aliphatic alcohol, commonly known as benenyl alcohol, which is a white waxy solid having a melting point of between 70° and 72° C. It has the molecular formula $C_{22}H_{46}O$ and a molecular weight of 326.61. The structure of *n*-docosanol is:



(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review was conducted under Sec. 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355), pursuant to the regulations set forth in 21 C.F.R. 314.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred.

The approved product received permission for commercial marketing or use under Sec. 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) on July 25, 2000. A copy of the approval letter received from the FDA is attached as **Exhibit C**.

(4) An identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone

or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in Abreva™ is the above-described aliphatic alcohol (docosanol), which has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

This application is being submitted on or before September 25, the last day of the sixty-day period permitted for submission pursuant to 37 C.F.R. § 1.720(f), i.e. the last day of the sixty-day period following the July 25, 2000 approval for commercial marketing of Abreva™, that is not a Saturday, Sunday, or Federal holiday, as provided in 35 U.S.C. § 156 (d) (1); 37 C.F.R. § 1.720(f) and 37 C.F.R. § 1.7.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

This application seeks extension for U. S. Patent No. 4,874,794, issued to David H. KATZ on October 17, 1989. The patent will expire on April 28, 2009.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of U. S. Patent No. 4,874,794, including claims and drawings, is enclosed as **Exhibit D**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

Copies of the Maintenance Fee Statements for the first and second maintenance fee payments are enclosed as **Exhibit E**.

U. S. Patent No. 4,874,794 has not been subject to any disclaimer, certificate of correction, or reexamination.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product.

The approved product is the active ingredient in Abreva™, 10% docosanol. Claim 1 encompasses a method of using the approved product for treating virus-induced and inflammatory diseases of skin and membranes in humans or animals. The relationship between the Claim 1 of U. S. Patent No. 4,874,794 and methods of using the approved product is as follows:

Claim 1. A method treating virus-induced and inflammatory diseases of skin and membranes in humans or animals is recited, comprising topical application of a composition consisting of one or more of the aliphatic alcohols docosanol, tetraconsanol and hexacosanol in a concentration of from 0.1 to 25 percent by weight in a physiologically compatible carrier to the inflamed skin or membrane of the patient to be treated.	**Approved product and method of using:** Abreva™ (10% docosanol) was approved for treating cold sores (fever blisters), which are inflammatory skin conditions that may be induced by viral infection. Topical application of a composition consisting of 10% docosanol was approved in a physiologically compatible cream. Docosanol is one of the three aliphatic alcohols recited in Claim 1. The approved concentration of 10% is encompassed by the recited concentration range of from 0.1 to 25 percent by weight.

(10) ***A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. 156 (g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period, particularly, for a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued.***

The following dates and related information are applicable for the new drug application (NDA) approval of Abreva™:

Date of IND:	July 11, 1991
IND Number:	37,321
Submission Date of NDA:	December 22, 1997 for acceptance of the completed NDA; a presubmission of drug substance, drug product and environmental assessment information, and nonclinical pharmacology, toxicology and pharmacokinetics was made on November 25, 1997.
FDA Approval Date for NDA:	July 25, 2000
NDA Number:	20-941

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The regulatory review period began on July 11, 1991 with the submission of the IND. During the period beginning July 11, 1991, and continuing through July 25, 2000, efforts were underway by AVANIR Pharmaceuticals, the marketing applicant, to gain approval of the New Drug Application (NDA), which was filed in stages beginning November 25, 1997 and completed on December 22, 1997.

During this period, the following significant activities and dates are applicable:

Date	Activity
July 11, 1989	Submit IND.
August 26, 1991	Submit supplement (001) to IND application 37,321 with results of *in vitro* and *in vivo* studies of docosanol effects on HSV-1 and HSV-2 infection.
February 12, 1992	Letter to FDA (002) with additional data regarding pharmacology, toxicology and microbiology.
March 16, 1992	Letter to FDA (003) regarding information amendment with additional data regarding chemistry and microbiology.
April 2, 1992	Letter to FDA (004) with additional data regarding pharmacology, toxicology and clinical.
April 9, 1992	Letter to FDA (005) regarding new protocol for Phase II clinical investigation.
April 15, 1992	Letter to FDA (006) regarding amendment to Report of RCC.

June 19, 1992	Letter to FDA (007) regarding Information amendment (chemistry/microbiology) and Protocol amendment (change in protocol).
July 15, 1992	Letter to FDA (008) regarding chemistry, manufacturing and controls.
September 17, 1992	Letter to FDA (009) regarding topical cream formulation.
September 25, 1992	Letter to FDA (010) regarding investigator's brochure and new protocol for Phase II clinical investigation.
October 6, 1992	Letter to FDA (011) regarding protocol amendment, information amendment, and response to FDA request for information.
November 6, 1992	Letter to FDA (012) regarding protocol amendment and Annual Report.
December, 1992 – June, 1993	Randomized, double-blind, steric acid placebo-controlled study (92-LID-02).
January 12, 1993	Letter to FDA (013) regarding Protocol amendment and Information amendment.
March 14, 1993 – March 6, 1995	Phase II, randomized, double-blind, steric acid placebo-controlled study (92-LID-04).
March 24, 1993	Letter to FDA (014) regarding change in protocol 92-LID-04, Information amendment, clinical protocol, IRB approval, and IRB approved consent form.
January 20, 1994	Letter to FDA (015) regarding Annual Report for 10% docosanol cream.
January 27, 1994	Letter to FDA (016) regarding amendment to 92-LID-03 and 92-LID-04, and amendment to information (chemistry/microbiology).
March, 1994 – March, 1995	Randomized, double-blind, docosanol vs. acyclovir 5% cream study (94-LID-01).
June 9, 1994	Letter to FDA (017) regarding overview of package and package for end of Phase II meeting, with formulation development history, ADME studies, toxicology studies, carcinogenicity rationale, Phase I safety studies, Phase II clinical studies and Phase III clinical program.
June 22, 1994	Letter to FDA (018) regarding complete protocols for toxicology and metabolic studies.

July 5, 1994	Letter to FDA (019) regarding IRB approval, 94-LID-01 brochure/protocol, 92-LID-02 reports and completed acute toxicology studies.
July 13, 1994	Letter to FDA (020) regarding response to request for information.
August 2, 1994	Letter to FDA (021) regarding response to request for information.
September 7, 1994	Letter to FDA (022) regarding end of Phase II meeting minutes.
September 21, 1994	Letter to FDA (023) regarding revised protocols 92-LID-04 and new protocols 94-LID-01 and 94-LID-03; IRB approval.
September 23, 1994	Letter to FDA (024) regarding Adverse Events Report.
November 8, 1994	Letter to FDA (025) regarding revised protocols 94-LID-04 and 94-LID-05.
November 15, 1994	Letter to FDA (026) regarding regulatory status of Phase III protocols.
November 17, 1994	Letter to FDA (027) regarding transfer of monitoring responsibility to CRO.
December 5, 1994	Letter to FDA (028) regarding response to end of Phase II meeting pharm/tox issues and carcinogenicity testing.
December 8, 1994	Letter to FDA (029) regarding absorption of labeled docosanol in cream formula 3.
December 12, 1994 – August 17, 1995	Clinic-initiated, double-blind, steric acid placebo-controlled study (94-LID-04).
December 15, 1994 – October 27, 1995	Clinic-initiated, double-blind, steric acid placebo-controlled study (94-LID-05).
January 5, 1995	Letter to FDA (030) regarding new investigators.
January 30, 1995	Letter to FDA (031) regarding Annual Report.
February 14, 1995	Letter to FDA (032) regarding ADME and Toxicology Program for docosanol 10% cream.
March 8, 1995	Letter to FDA (033) regarding 92-LID-04 Safety report and 94-LID-04 & 05 new investigators.
May 4, 1995 – October 20, 1995	Clinic-initiated, double-blind, steric acid placebo-controlled study (95-LID-10).

March 27, 1995	Letter to FDA (035) regarding new protocol 95-LID-10, amended protocols 94-LID-04 & 05, and summary of changes for 94-LID-04 & 05.
May 5, 1995	Letter to FDA (036) regarding new protocols, 95-LID-03a,b,c and completed toxicology study final report.
June 8, 1995	Letter to FDA (038) regarding 95-LID-10 new investigators and transfer to CRO and 95-LID-03a amended protocol
July 26, 1995	Letter to FDA (039) regarding amended protocols and summaries of changes for studies 95-LID-10, 94-LID-05 and 94-LID-04.
October 31, 1995	Letter to FDA (040) regarding Annual Report of docosanol 10% cream
November 21, 1995	Letter to FDA (041) regarding revised statistical sections for studies 95-LID-10, 94-LID-05 and 94-LID-04.
February 7, 1996	Letter to FDA (043) regarding final reports for LAK/015, 010, 009, 011, 013, 014 and 6634-100.
February 14, 1996	Letter to FDA (046) regarding demographic data for 95-LID-10, 94-LID-05, 94-LID-04 and 92-LID-04 studies.
March 5, 1996	Letter to FDA (047) regarding final reports for 95-LID-03a, b, and c.
April 10, 1996	Letter to FDA (048) regarding placebo formulation issues.
July 29, 1996 – April 21, 1997	Clinic-initiated, double-blind, placebo-controlled multicenter study to assess safety and efficacy of topical docosanol 10% cream (96-LID-06).
May 2, 1996	Letter to FDA (049) regarding IRB approval of 95-LID-KS and MC and amended protocols.
June 10, 1996	Letter to FDA (050) regarding new protocols 95-LID-KS2 and MC2.
June 19, 1996	Letter to FDA (053) regarding amended protocol 95-LID-KS and summary of changes.
July 31, 1996	Letter to FDA (055) regarding amended protocol 95-LID-06 and summary of changes.
August 15, 1996	Letter to FDA (056) regarding amended protocol 95-LID-07 and summary of changes, new investigators and glossary of terms.

September 17, 1996	Letter to FDA (057) regarding modified consent forms.
October 14, 1996 – May 12, 1997	Clinic-initiated, double-blind, placebo-controlled multicenter study to assess safety and efficacy of topical docosanol 10% cream (96-LID-07).
October 18, 1996	Letter to FDA (058) regarding new investigators.
November 5, 1996	Letter to FDA (059) regarding IND safety reports for 95-LID-KS and MC.
December 10, 1996	Letter to FDA (060) regarding Annual Report.
December 20, 1996	Letter to FDA (061) regarding integrated clinical statistical report for 94-LID-04.
January 16, 1997	Letter to FDA (062) regarding studies LAK/006,012, 015, 018, 008, and 48B-L-20.
February 5, 1997	Letter to FDA (063) regarding integrated clinical statistical report for 94-LID-10.
February 21, 1997	Letter to FDA (064) regarding combined analysis of studies 96-06 and 96-07.
March 10, 1997	Letter to FDA (065) regarding KGL protocol, IRB approval, and consent form.
March 27, 1997	Letter to FDA (066) regarding revised protocol 96-LID-06 and 07.
March 28, 1997	Letter to FDA (067) regarding integrated clinical statistical report for 94-LID-05.
April 29, 1997	Letter to FDA (068) regarding final reports for 94-LID-01, 02 and 03.
August 2, 1997	Letter to FDA (069) regarding integrated clinical statistical report for 92-LID-03.
August 8, 1997	Letter to FDA (070) regarding integrated clinical statistical report for 95-LID-KS.
October 8, 1997	Letter to FDA (072) regarding pre-NDA meeting.
November 25, 1997	File NDA presubmission (075) drug substance, drug product and environmental assessment information, and nonclinical pharmacology, toxicology and pharmacokinetics.
December 22, 1997	Submit complete NDA (20-941).
December 22, 1998	Not-approvable letter received from FDA.
January 13, 1999	Letter to FDA requesting meeting to submit additional evidence of effectiveness.
February 26, 1999	Letter to FDA regarding Briefing Document for meeting to discuss non-approval letter.
March 1, 1999	Briefing Document sent to FDA in advance of meeting.

March 18, 1999	Letter to FDA regarding response to request for amendment to NDA regarding chemistry, microbiology and pharmacology/toxicology comments.
March 24, 1999	Submit Amendment to NDA.
March 29, 1999	Submit Amendment to NDA regarding additional evidence of effectiveness.
April 30, 1999	Response to FDA questions regarding clinical study 92-LID-02.
May 5, 1999	Letter to FDA with statistical information requested by reviewing statistician.
May 14, 1999	Letter to FDA with completed TABLE A of Briefing Document and request for meeting on biostatistical issues.
May 24, 1999	Letter to FDA with request for expedited review by the Labeling and Nomenclature Committee and submission of revised product labeling.
June 8, 1999	Meeting with FDA statisticians to discuss additional evidence of effectiveness.
June 25, 1999	Letter to FDA regarding statistical issues.
August 3, 1999	Letter to FDA with response to question regarding suggested statistical analysis.
September 24, 1999	FDA informs AVANIR that available clinical data is insufficient to establish effectiveness.
September 30, 1999	Letter to CDER Ombudsman regarding chronology of events and AVANIR/FDA communications.
October 13, 1999	File formal dispute resolution request.
October 29, 1999	Teleconference with FDA indicating that 92-LID-02 will be sufficient as a second study to consider docosanol cream as an OTC.
November 22, 1999	FDA requests additional information.
December 2, 1999	File complete response to FDA request for additional information.
December 9, 1999	Audit of clinical study 92-LID-02 completed, form 483 issued.
January 21, 2000	Submitted form 483 response.
May 30, 2000	Approvable letter received from FDA, pending finalization of acceptable labeling.
June 6, 2000	Letter to FDA regarding various product OTC labels.
June 12, 2000	Letter to FDA regarding formal Dispute Resolution Request (regarding labeling).
July 25, 2000	Marketing approval letter received from FDA.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

AVANIR Pharmaceuticals believes that it is entitled to an extension of term for U. S. Patent No. 4,874,794 (the Patent) in accordance with the provisions of 35 U.S.C. § 156. AVANIR Pharmaceuticals believes that the period of extension applicable to the patent is 5 years (1826 days), based on the following calculation in accordance with 37 C.F.R. § 1.775 (subsections listed below):

(c) The length of the regulatory review period for the approved product is calculated as the sum of:

(1) The number of days in the period beginning on the date of exemption under 35 U.S.C. §156(g)(1)(B)(i) from July 11, 1991 (the effective date of the IND) until December 22, 1997 (the NDA submission date) which is 2356 days; and

(2) The number of days in the review period under 35 U.S.C. §156(g)(1)(B)(i) from December 22, 1997 (the NDA submission date) until July 25, 2000 (marketing approval date), which is 946 days.

Thus, the total regulatory review period under 37 C.F.R. § 1.775(c) is 3302 days.

(d) The term is determined as follows:

(1) The sum of the following is subtracted from the regulatory review period (3302 days) as determined above:

(i) The number of days in the regulatory review period which were on or before the date on which the Patent issued. As the regulatory review commenced after the Patent issued, the number of days is 0 days.

(ii) The number of days in the regulatory review period wherein the Applicant did not act with due diligence, which is 0 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) (2356 days) that has been reduced in accordance with the two items above, which is 2356 ÷ 2 = 1178 days.

Thus, the term under subsection (d) is 3302 days – 1178 days = 2124 days.

(2) The date of expiration of the patent is extended by adding the number of days determined in (d)(1) (2124 days) to the original term of the patent, i.e., April 28, 2009 plus 2124 days, or February 20, 2015.

(3) Add 14-years to the date of approval (July 25, 2000), which would be July 25, 2014.

(4) Compare the dates of expiration obtained under paragraph (d)(2) and (d)(3) above and select the earlier date. Accordingly, July 25, 2014 is earlier than February 20, 2015.

(5) U.S. Patent No. 4,874,794 issued on October 17, 1989, which is after September 24, 1984. Accordingly, paragraph (5) is applicable.

(i) Add 5 years to the date of expiration of the patent (April 28, 2009), which would be April 28, 2014.

(ii) Compare the dates of expiration obtained under paragraphs (d)(4) and (d)(5)(i) above and select the earlier date. Accordingly, April 28, 2014 is earlier than July 25, 2014.

Thus, a 5-year extension from the original date of expiration is the maximum allowable extension available to AVANIR on U.S. Patent No. 4,874,794 under 37 C.F.R. §1.775.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (37 C.F.R. §1.765).

AVANIR Pharmaceuticals acknowledges a duty to disclose to the Commissioner of Patents and Trademarks (and to the Patent and Trademark Office), and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (37 C.F.R. § 1.20 (j)).

AVANIR Pharmaceuticals hereby encloses a check in the amount of $1,120.00, the prescribed fee under 37 C.F.R. § 1.20 (j). If for any reason this payment is insufficient, applicant

hereby authorizes that any deficiency may be charged, or any overpayment credited, to Deposit Account No. 11-1410.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please direct all correspondence relating to this application to:

Mark R. Benedict
Registration No. 44,531
Attorney of Record
620 Newport Center Drive, Sixteenth Floor
Newport Beach, CA 92660
Telephone: (949) 760-0404
Direct line: (949) 721-6323
Facsimile: (949) 760-9502
E-mail: mbenedict@kmob.com

(16) A duplicate of the application papers, certified as such.

AVANIR Pharmaceuticals hereby certifies that this application for patent term extension and supporting papers is being filed in duplicate, and certifies that the copy is a true copy of the original application and supporting papers.

(17) An oath or declaration.

A Declaration as set forth in 37 C.F.R. §1.740 (b) accompanies the present Application as **Exhibit F.**

If this application for extension of patent term is held to be informal, AVANIR Pharmaceuticals may seek to have the holding reviewed by filing a petition with the required fee, as necessary, pursuant to 37 C.F.R. § 1.181 or 1.183, as appropriate, within such time as may be set in any notice that the application has been held to be informal, or if no time is set, within one month of the date on which the application was held informal.

Patent No : **U.S. 4,874,794**
Issued : **October 17, 1989**

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 9/22/00

By: _____

Mark R. Benedict
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Sixteenth Floor
Newport Beach, CA 92660
(949) 760-0404

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nai/MRB

Exhibit A

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

JUNE 29, 1999

PTAS

101021377A

KNOBBE,MARTINS, OLSON, ET AL.
DANIEL E. ALTMAN
620 NEWPORT CENTER DRIVE
SIXTEENTH FLOOR
NEWPORT BEACH, CA 92660

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 04/20/1999

REEL/FRAME: 9901/0274
NUMBER OF PAGES: 5

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
LIDAK PHARMACEUTICALS

DOC DATE: 11/20/1998

ASSIGNEE:
AVANIR PHARMACEUTICALS
9393 TOWNE CENTRE DR., #200
SAN DIEGO, CALIFORNIA 92121

SERIAL NUMBER: 08916624
PATENT NUMBER:

FILING DATE: 08/22/1997
ISSUE DATE:

SERIAL NUMBER: 09978213
PATENT NUMBER:

FILING DATE: 08/22/1997
ISSUE DATE:

SERIAL NUMBER: 07345084
PATENT NUMBER: 4874794

FILING DATE: 04/28/1989
ISSUE DATE: 10/17/1989

SERIAL NUMBER: 07431304
PATENT NUMBER: 5071879

FILING DATE: 11/02/1989
ISSUE DATE: 12/10/1991

NO DATES DOCKETED
ATTORNEY RESPONSIBLE
INITIAL _____

SERIAL NUMBER: 07430822 FILING DATE: 11/02/1989
PATENT NUMBER: 5070107 ISSUE DATE: 12/03/1991

SERIAL NUMBER: 08299944 FILING DATE: 09/02/1994
PATENT NUMBER: 5534554 ISSUE DATE: 07/09/1996

SERIAL NUMBER: 08065640 FILING DATE: 05/21/1993
PATENT NUMBER: 5296514 ISSUE DATE: 03/22/1994

SHARON LATIMER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

Client Code: AVANIR

RECORDATION FORM COVER SHEET
PATENTS ONLY

TO THE ASSISTANT COMMISSIONER FOR PATENTS: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies): (If multiple assignors, list numerically)

Lidak Pharmaceuticals

Additional name(s) of conveying party(ies) attached?
( ) Yes (X) No

2. Name and address of receiving party(ies):

Name: Avanir Pharmaceuticals
Internal Address:
Street Address: 9393 Towne Centre Dr., #200
City: San Diego **State:** CA **ZIP:** 92121

Additional name(s) of receiving party(ies) attached?
( ) Yes (X) No

---

3. Nature of conveyance:

( ) Assignment
(X) Change of Name
( ) Other:

Execution Date: (If multiple assignors, list execution dates in numerical order corresponding to numbers indicated in 1 above)

November 20, 1998

4. Application numbers or Patent numbers:

( ) Application(s) filed herewith Execution Date(s):

(X) Patent Application No.: See Attachment A
Filing Date:

(X) Patent No.: See Attachment B
Issue Date:

Additional numbers attached? (X) Yes ( ) No

---

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Daniel E. Altman
KNOBBE, MARTENS, OLSON & BEAR, LLP
Customer No. 20,995
Internal Address: Sixteenth Floor
Street Address: 620 Newport Center Drive
City: Newport Beach **State:** CA **ZIP:** 92660
Attorney's Docket No.: AVANIR

6. Total number of applications and patents involved: 7

7. Total fee (37 CFR 3.41): $280

(X) Enclosed
(X) Authorized to be charged to deposit account if any additional fees are required, or to credit any overpayment

8. Deposit account number: 11-1410

Please charge this account for any additional fees which may be required, or credit any overpayment to this account.

---

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct, and any attached copy is a true copy of the original document.

Daniel E. Altman
Name of Person Signing

Daniel Altman
Signature

16 April 1999
Date

34,115
Registration No.

Total number of pages including cover sheet, attachments and document: 5

Mail documents to be recorded with required cover sheet information to:

Assistant Commissioner for Patents
Box Assignments
Washington, D.C. 20231

MRB-1454:dd
041699

KNOBBE, MARTENS, OLSON & BEAR, LLP
620 NEWPORT CENTER DR 16TH FLOOR NEWPORT BEACH, CA 92660
(949) 760-0404 FAX (949) 760-9502

ATTACHMENT A

Our Reference No.	Application No.	Filing Date
AVANIR.051A2	08/916,624	08/22/97
AVANIR.054A2	09/978,213	11/25/97

ATTACHMENT B

Our Reference No.	Patent No.	Issue Date
AVANIR.024A	4,874,794	10/17/89
AVANIR.026A	5,071,879	12/10/91
AVANIR.027A	5,070,107	12/03/91
AVANIR.030CP1	5,534,554	07/09/96
AVANIR.043CP1	5,296,514	03/22/94

A0517081

State of California

SECRETARY OF STATE

I, *BILL JONES*, Secretary of State of the State of California, hereby certify:

That the attached transcript of 1 page(s) has been compared with the record on file in this office, of which it purports to be a copy, and that it is full, true and correct.

IN WITNESS WHEREOF, I execute this certificate and affix the Great Seal of the State of California this day of

NOV 30 1998

Bill Jones

Secretary of State

Sec/State Form CE-107 (rev. 9/98)

OSP 98 13524

A0517081

ENDORSED-FILED
IN THE OFFICE OF THE
SECRETARY OF STATE
OF THE STATE OF CALIFORNIA

NOV 24 1998

BILL JONES, SECRETARY OF STATE

CERTIFICATE OF AMENDMENT OF THE ARTICLES OF INCORPORATION OF LIDAK PHARMACEUTICALS, a California Corporation

Gerald J. Yakatan, Ph.D. and Gregory P. Hanson certify that:

1. They are the President and CEO; and V.P., Finance, Chief Financial Officer and Secretary, respectively, of LIDAK Pharmaceuticals (the "Corporation").

2. ARTICLE 1 of the Articles of Incorporation of the Corporation is hereby restated to read as follows:

"ARTICLE 1

The name of the corporation is AVANIR Pharmaceuticals (the "Corporation")."

3. The foregoing amendment of the Articles of Incorporation has been duly approved by the Corporation's Board of Directors.

4. The foregoing amendment of the Articles of Incorporation has been duly approved by a vote of the shareholders of the Corporation in accordance with Section 902 of the California Corporations Code. The total number of outstanding shares of the Corporation entitled to vote with respect to the amendment was 39,814,017 shares of Class A Common Stock (one vote per share), and 49,000 shares of Class B Common Stock (five votes per share). Class A Common Stock and Class B Common Stock voted together as Common Stock with respect to the foregoing amendment. The number of shares voting in favor of the amendment equaled or exceeded the vote required. The percentage vote required was more than 50% of the votes entitled to be cast.

We further declare, under penalty of perjury under the laws of the State California, that the matters set forth in this Certificate of Amendment of the Articles of Incorporation of LIDAK Pharmaceuticals. are true and correct of our own knowledge.

Executed at San Diego, California on this 20th day of November, 1998.

Gerald J. Yakatan, Ph.D., President and CEO

Gregory P. Hanson, V.P., Finance, Chief Financial Officer and Secretary

OFFICE OF THE SECRETARY OF STATE

500982v1

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TO: GRANT L. HUBBARD
300 SO. HARBOR BLVD., STE. 805
ANAHEIM, CA 92805

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

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ASSIGNOR: 001 KATZ, DAVID H. DOC DATE: 03/29/90

RECORDATION DATE: 04/06/90 NUMBER OF PAGES 006 REEL/FRAME 5293/0061

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 LIKAK PHARMACEUTICALS, 11077 NORTH TORREY PINES ROAD, LA JOLLA, CA 92037 A CA CORP.

SERIAL NUMBER 7-345084 FILING DATE 04/28/89
PATENT NUMBER 4,874,794 ISSUE DATE 10/17/89

Anaheim, California 92805

Registration No. 24193

Best Available Copy

Attorney's Docket No. LIDAK-024A

(Rd.28-11/85 Pub.605) **FORM 16-5** 16-13

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☐ In re application of*:

Serial No. Group No.

Filed: Examiner:

For*:

☒ **Patent:** 4,874,794 Issued: 17 October 1989

*NOTE: *Insert name(s) of inventor(s) and title also for patent. Where recordal is with respect to a maintenance fee payment also insert application serial number and filing date and add Box M. Fee to address.*

Commissioner of Patents and Trademarks

Washington, D.C. 20231

RECORDAL OF ASSIGNMENT (37 CFR 1.331)

1. Kindly record the enclosed assignment for the above identified
   - ☐ application
   - ☒ patent
2. When recordal has been effected, please return the original assignment document to the undersigned.
3. Fee Payment
   - ☒ Attached is a check in the sum of $XXX8.00
   - ☐ Charge Account No. _____ the sum of $7.00. A duplicate of this recordal request is attached.

NOTE: 37 CFR 1.21(h). Recording of documents: (1) For recording each assignment, agreement or other paper relating to the property in a patent or application $7.00; (2) Where a document to be recorded refers to more than one patent or application, for each additional patent application $2.00.

Tel. No. (714) 491-9076

Reg. No. 24,193

SIGNATURE OF ATTORNEY

Grant L. Hubbard

Type or print name of attorney

300 S. Harbor Blvd., Ste. 805

P.O. Address

Anaheim, CA 92805

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

Dawn M. Cook

(Type or print name of person mailing paper)

Date: 4/2/90

REEL 3963 FRAME 063

Attorney's Docket No. LIDAK-024A

(Rev.27-7/85 Pub.405) FORM 16-3 16-7

PATENT

For: ☒ U.S. and/or ☒ Foreign Rights
For: ☐ U.S. Application or ☒ U.S. Patent
By: ☐ Inventor(s) or ☒ Present Owner

ASSIGNMENT OF INVENTION

In consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration,

ASSIGNOR: (inventor(s) or person(s) or entity(ies) who own the invention)

LIDAK BIOPHARMACEUTICALS
(Type or print name(s) of ASSIGNOR(S))

11077 North Torrey Pines Road
Address

La Jolla, CA 92037

California Corporation
Nationality

(If assignment is by person or entity to whom invention was previously assigned and this was recorded in PTO add the following)

Recorded on 04/28/89
Reel 5068
Frame 0229

hereby sells, assigns and transfers to

ASSIGNEE:

LIDAK PHARMACEUTICALS
(Type or print name of ASSIGNEE)

11077 North Torrey Pines Road
Address

La Jolla, CA 92037

California Corporation
Nationality

and the successors, assigns and legal representatives of the ASSIGNEE

(complete one of the following)

☒ the entire right, title and interest

☐ an undivided _____ percent (_____%) interest

for the United States and its territorial possessions

(check the following box if foreign rights are also to be assigned)

☒ and in all foreign countries

in and to, any and all improvements which are disclosed in the invention entitled:

INFLAMMATORY DISEASE TREATMENT

(check and complete (a), (b), (c) or (d))

and which is found in

(a) ☐ U.S. patent application executed on even date herewith

(b) ☐ U.S. patent application executed on _____

(c) ☐ U.S. application serial no. _____ filed on _____

(d) ☒ U.S. patent no. 4,874,794 issued 10/17/89

(also check (e) if foreign application(s) is also being assigned)

(e) ☒ and any legal equivalent thereof in a foreign country, including the right to claim priority

and, in and to, all Letters Patent to be obtained for said invention by the above application or any continuation, division, renewal, or substitute thereof, and as to letters patent any re-issue or re-examination thereof

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said invention and said Letters Patent and legal equivalents as may be known and accessible to ASSIGNOR and will testify as to the same in any interference, litigation or proceeding related thereto and will promptly execute and deliver to ASSIGNEE or its legal representatives any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalents thereof which may be necessary or desirable to carry out the purposes thereof.

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this X March 29, 1990 (Date of signing).

WARNING: Date of signing must be the same as the date of execution of the application if item (a) was checked above.

X _____
Signature of ASSIGNOR(S)

_____

_____

_____

_____

_____

_____

If ASSIGNOR is a legal entity complete the following information

David H. Katz, M.D.
Type or print the name of the above person authorized to sign on behalf of ASSIGNOR

Chairman and Chief Executive Officer
Title

NOTE: No witnessing, notarization or legalization is necessary. If the assignment is notarized or legalized then it will only be prima facie evidence of execution 35 USC 261. Use next page if notarization is desired.

☒ Notarization or Legalization Page Added.

NOTARIZATION OR LEGALIZATION ACCOMPANYING ASSIGNMENT

NOTE: Executing this page is not required for assignment and is only prima facie evidence of execution. 35 USC 261.

Details of Country and place of signing of assignments

County of San Diego

State of California

Before me this 29th day of March 1990 personally appeared the above named individual(s), to me known to be the person(s) who ☒ is ☐ are described in and who executed the foregoing assignment instrument and acknowledged to me that

☒ he		☒ his
☐ she	executed the same of	☐ her
☐ they		☐ their

own free will for the purpose therein expressed

OFFICIAL SEAL
BONNIE L. ELBIK
NOTARY PUBLIC - CALIFORNIA
SAN DIEGO COUNTY
My Comm. Expires May 14, 1993

/s/ Bonnie L. Elbik
Notary Public or Consular Officer of the United States of America

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OFFICE

APR - 6 1990

REEL 5293 FRAME 066

B

Retain this carton for full product uses, directions and warnings.

abreva®

Drug Facts

Active Ingredient — **Purpose**

Docosanol 10% ..... Cold sore/fever blister treatment

Uses
- treats cold sores/fever blisters on the face or lips
- shortens healing time and duration of symptoms:
  - tingling, pain, burning, and/or itching

Warnings

For external use only

Do not use
- if you are allergic to any ingredient in this product

When using this product
- apply only to affected areas
- do not use in or near the eyes
- avoid applying directly inside your mouth
- do not share this product with anyone. This may spread infection.

Stop use and ask a doctor if
- your cold sore gets worse or the cold sore is not healed within 10 days

Keep out of reach of children. If swallowed, get medical help or contact a poison control center right away.

Directions
- adults and children 12 years or over:
  - wash hands before and after applying cream
  - apply to affected area on face or lips at the first sign of cold sore/fever blister (tingle). Early treatment ensures the best results.
  - rub in gently but completely
  - use 5 times a day until healed
- children under 12 years: ask a doctor

3 0766-0801-00 9

Other information
- store at 20°-25°C (68°-77°F)
- do not freeze

Inactive Ingredients benzyl alcohol, light mineral oil, propylene glycol, purified water, sucrose distearate, sucrose stearate

Questions? call 1-877-709-3539 weekdays

abreva®
DOCOSANOL 10% CREAM
COLD SORE/FEVER BLISTER TREATMENT
NET WT 2.0g (.07 oz)
LOT

NEW
COLD SORE TREATMENT

abreva®

Shortens healing time and duration of symptoms

Cream formula - dries clear

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

C

NDA 20-941

JUL 25 2000

Avanir Pharmaceuticals
Attention: James E. Berg
Vice President of Clinical Affairs and Product Development
9393 Towne Centre Drive
Suite 200
San Diego, CA, 92121

Dear Mr. Berg:

Please refer to your new drug application (NDA) dated December 19, 1997, received December 22, 1997, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abreva (docosanol) Cream, 10% .

We acknowledge receipt of your submissions dated June 6, 12, July 21, and 25, 2000. Your submission of June 6, 2000 constituted a complete response to our May 30, 2000 action letter.

This new drug application provides for the use of Abreva Cream, 10% (docosanol) for cold sore/fever blister treatment.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (immediate container and carton labels submitted July 21, 2000 and amended by your July 25 fax) and must be formatted in accordance with the requirements of 21 CFR 201.66. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternately, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-941." Approval of this submission by FDA is not required before the labeling is used.

You are cautioned not to promote the product as an antiviral or as providing symptomatic relief of cold sores. Promotion of symptomatic benefit should be limited to the information provided in labeling, that the product shortens healing time and duration of symptoms.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Babette Merritt, Project Manager, at (301) 827-2222.

Sincerely,

Robert J. DeLap

Robert J. DeLap, M.D., Ph.D.
Director Office of Drug Evaluation V
Center for Drug Evaluation and Research

8 2000

The United States of America

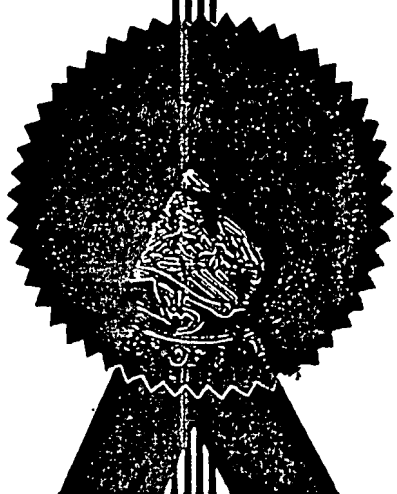
The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.



Commissioner of Patents and Trademarks

NOTICE

If the application for this patent was filed on or after December 12, 1980, maintenance fees are due three years and six months, seven years and six months, and eleven years and six months after the date of this grant, or within a grace period of six months thereafter upon

United States Patent [19]

Katz

[11] **Patent Number: 4,874,794**

[45] **Date of Patent: Oct. 17, 1989**

[54] **INFLAMMATORY DISEASE TREATMENT**

[75] Inventor: **David H. Katz, La Jolla, Calif.**

[73] Assignee: **Lidak Biopharmaceuticals, La Jolla, Calif.**

[21] Appl. No.: **345,084**

[22] Filed: **Apr. 28, 1989**

[51] **Int. Cl.**[4] **A61V 31/045**

[52] **U.S. Cl.** **514/724**

[58] **Field of Search** **514/724**

Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Grant L. Hubbard

[57] **ABSTRACT**

A method treating virus-induced and inflammatory diseases of skin and membranes in humans or animals, comprising application of a composition consisting of one or more of the aliphatic alcohols docosanol, tetracosanol and hexacosanol in a physiologically compatible carrier is disclosed.

2 Claims, No Drawings

INFLAMMATORY DISEASE TREATMENT

FIELD OF THE INVENTION

This invention relates to alcohol-containing compositions which are useful in treating virus infections and inflammatory diseases of the skin and membranes, including burns, laceration damage and acute injuries. More specifically the present invention relates to a naarrow class of oaliphatic straightchain saturated monohydric alcohols which have from 20 to 26, preferably 22 to 26, carbons in the chain.

BACKGROUND OF THE INVENTION

It is well-known that certain selected alcohols have some physiological activity. It is known, for example, that 1-triacontanol stimulates the growth of plants, see, e.g. Ries, Stanley K. and Sweeney, Charles C., U.S. Pat. No. 4,150,970. Interestingly, the C-30 aalcohol triacontanol appears to possess this physiologicl activity and that the C-28 and C-32 do not possess such physiological activity, or at least have very much less physiological activity in plant growth, see, e.g., the patents and publications of Ries et al., ibid, and of Ashmead, Harvey H., Weleber, Andrew J., Laughlin, Robert G., Nickey, Donald O. & Parker, Dane. K, and Ohorogge, Alvin J.

Triacontanol has also been reported to accelerate the decomposition of sewage and reduce H.S, Starr, Jerry, U.S. Pat. No. 4,246,100.

Beeswax comprises, inter alia, esters of long-chain aliphatic alcohols having chain lengths in the area of interest, and it is known to obtain such alcohols by hydrolysis of beeswax. Beeswax has been used sicne antiquity in a great variety of cosmetic and thereapeutic applications, as a bse for lipstick, in lotions and creams, as an emollient and as a constituent in therapeutic products for topical and membrane application. Various constituents of beeswax and products derived from beeswax have also been used in cosmetic and therapeutic applications. For example, Slimak, Karen M., U.S. Pat. No. 4,793,991, describes a hypoallerginic cosmetic comprising single plant source beeswax. Gans, Eugen, Nacht, Sergio and Yeung, David have described the use of the non-polar saturated straight chain C-21 to C-33 hydrocarbon fraction of beeswax in the treatment of inflammatory skin disorders, U.S. Pat. No. 4,623,667.

The mechanism of the rather diverse and upredictable physiological effects of the vaarious alcohols are, at best, poorly understood and studies are not generally definitive. There appears to some interaction of certain nalkanols with lipid bilayer membranes, Westerman, PW, Pope, JM, Phonphok, N., Dan, JW, dubro, DW, *Biochim Biophys Acta* (NETHERLANDS) 939, 64–78 (1988), and studies have been conducted respecting the partitioning of long-chain alcohols into lipid bilayers, Franks NP & Lieb WR, *Proc. Natl. Acad. Sci.* USA 83 5116–20 (1986); cholesterol solubility of n-alkanols, Pal S. & Moulik SP, *Indian J Biochem Biophys* 24 24–8 (1987); neurological effects of certain long-chain alcohols, Natarajan V & Schmid HH, *Lipids* 12 128–30 (1977); Snider SR, *Ann Neurol* 16 723 (1984); Borg J, Toazara J. Hietter H, Henry M, Schmitt G, Luu B, *FEBS Lett* 213 406–10 (1987).

Levin, Ezra reported that tetracosanol, hexacosanol, octacosanol and triacontanol aand their esters improved physical performance of athletes and disclosed compositions comprising such alcohols and esters in vegetable oil bases for oral ingestion, U.S. Pat. No. 3,031,376.

An incidental disclosure of a composition intended for topical application comprising a major portion liquified gaseous propellant and a minor portion of a mixiture of C-12 to C-30 fatty alcohols which were used simply to mark the areas of application of the aerosol is contained in U.S. Pat. No. 3,584,115 to Gebhart.

Clark, U.S. Pat. No. 4,670,471 discloses the use of triacontanol, in a suitable carrier, as a treatment for inflammatory disorders such as herpes simplex, eczema, shingles, atopic dermatitis, psoriasis, etc. Clark performed experiments with the compositions of the type disclosed by Gebhart, U.S. Pat. No. 3,584,115 comprising an aerosol and a mixture of triacontanol and palmitic acid, which Clark indicates to be as effective as pure triacontanol, and concluded that the aerosol carrier destroyed the effect of triacontanol and that a hydrophilic carrier for triacontanol was necessary to achieve the desired anti-inflammatory effect. There is some reason to believe that Clark's composition was simply saponified beeswax which would contain triacontanol and palmitic acid, as Clark indicates, but which would also contain, as substantial constituents, hexacosanolic acid nd various hydrocarbons. Results of gas chromatographic-mass spectrum analysis of various compositions believed to have been used by Clark were not definitive, but suggested that at least some such compositions were very complex mixtures, some of which may be lower alkanes, esters, acids or alcohols. Whether or not these were found by Clark to be effective anti-inflammatory compositions is not known. McKeough, Mark & Spruance, SL evaluated the efficacy of 5 percent triacontanol in a branch chain ester base in the treatment of HSV-1 dorsal cutaneous infection in guinea pigs and concluded that the active ingredient in triacontanol is the long chain hydrocarbon (unpublished report in the file of U.S. Pat. No. 4,670,471).

Revici, Emanuel, Sherwood, Bob E., Benecke, Herman P., Rice, John M., and Geisler, Richard W., U.S. Pat. No. 4,513,008, disclose a method of inactivating developed virus using C-20 to C-24 polyunsaturated acids, aldehydes or alcohols having 5–7 double bonds, and references disclosures by Sands et al. (*Antimicrobial Agents and Chemotherapy* 15, 67–73 (1979)), antiviral acivity of C-14 to C-20 unsaturated alcohols having 1–4 double bonds, C-20 tetraenyl alcohol having low activity, Snipes et al., (*Antimicrobial Agents and Chemotherapy* 11, 98–104 (1977) and *Symp. Pharm. Effects Lipids* (*AOCS Monograph No.* 5) 63–74 (1978) even lower antiviral activity for saturated long-chain alcohols.

Katz, Martin & Neiman, Herbert M, U.S. Pat. No. 3,592,930 disclose a medicant vehicle containing from 15 to 45 parts of saturated fatty alcohol from 16 to 24 carbons, along with glycol solvent, plasticizer, penetrant and adjuvant which is used as a carrier for oantibiotics, steriods, antihistamines, etc.

Ryde, Emma Marta & Ekstedt, Jan Erik, U.S. Pat. No. 3,863,633 disclose a composition for topical treatament of the eye which comprises a lipophilic substance, a hydrophilic swellable polymer and from 10 to 80 percent C-12 to C-22 surface active alcohols such as 1-docossanol, 1-hexadecanol, 1-octadecanol and 1-eicosanol which serve as a stabilizer for the mixture.

The content of othe prior art and the corresponding skill of the art, relative to topically administered compositions, may be summarized as follows: Short-chain alcohols, i.e. under about 16 carbons, tend to be irritants

while longer chain alcohols, particularly the aliphatic alcohols tend to be non-irritating (Katz et al., supra). 1-Triacontanol, a 30-carbon unsaturated aliphatic alcohol, in a suitable hydrophilic carrier has (or may have depending upon the precise compositions used by Clark) value in treating inflammatory conditions of the skin (Clark, supra). Shorter chain C-10 to C-14 aliphatic alcohols demonstrate low level in vitro virucidal characteristics, while C-18 alcohols show noo discernable virucidal activity in vitro (Snipes, supra). Polyunsaturated C-20 to C-24 alcohols inactive enveloped virus (Revici et al., supra). C-16 to C-24 aliphatic alcohols are useful as stabilizers in carrier compositions for drugs having diverse physiological activity.

Respecting aliphatic alcohols, one would predict from the studies of Snipes and Clark that, in the continuum of aliphatic alcohols from C-10 to C-30 virucidal activity, at a very low level, may appear (if in vitro studies may be used to predict in vivo results) in C-10 to C-14 alcohols (which would also be irritants as reported by Katz), that virucidal activity disappears inthe C-16 to C-28 range and than appears uniquely (if Clark's compositions were pure triacontanol or mixtures of triacontanol with palmitic acid as he indicates) with the C-30 alcohol 1-triacontanol, which has been shown to have unique physiological effects in plant treatment.

Even considering the possible ambiguity of Clark's compositions, one would not predict any significant virucidal activity for aliphatic alcohols in the C-20 through C-28 chain-length.

Notwithstanding the negative teachings of the prior art, the present invention comprises compositions and methods for topical treatment of inflammatory diseases, including virus-induced inflammation, burns, laceration damage and acute injuries, in which the active constitute consists essentially of C-20 to C-26, and preferably C-22 to C-26 aliphatic alcohols, e.g. docosanol, tetracosanol and hexacosanol.

SUMMARY OF THE INVENTION

The present invention is embodied in a method treating inflammatory and viral skin diseases, such as may result, for example, from virus infection, burns, lacerations and acute injuries, comprising application of a composition consisting of one or more of C-20 to C-26 aliphatic alcohols, preferably one or more alcohols selected from the group consisting of 1-docosanol, 1-tetracosanol and 1-hexacosanol in a physiologically compatible carrier.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The compositions suitable for use in this invention consists essentially of a carrier which is physiologically compatible with the skin and membrane tissues of the patient, i.e. non-irritating, and which is substantially inactive physiologically (except for possible emollient properties) and, as the physiologically active composition, one or more C-20 to C-26 aliphatic alcohols, e.g. one or more of 1-eiconol, 1-docosanol, 1-tetracosanol and 1-hexacosanol.

The method may be carried out using compositions inwhich the sole physiologically active agent(s) is the C-20 to C-26 aliphatic alcohol, or comparable compositions which may also include other physiologically active constituents which do not interfere with the efficacy of the C-20 to C-26 alcohols.

The composition of the carrier is not critical so long as the carrier is non-irritating to skin and membranes and is substanatially free from physiological effect, e.g. has no physiological effect other than be an emollient.

An exemplary composition for use in this invention would be similar to that disclosed by Katz, et al. in U.S. Pat. No. 3,592,930 without the addition of any other physiologically active constituent, e.g. a mixiture of C-20 to C-26 alcohols, preferably one or more of the alcohols 1-docosanol, 1-tetracosanol and 1-hexacosanol, a glycol solvent such as propylene glycol, and, if desired, a plasaticizer such as glycerol or a polyethylene glycol having a molecular weight of from 800 to 20,000.

A suitable carrier may comprise white petrolatum, stearyl alcohol, isopropyl myristate, sorbitan monooleate, propylelne glycol, water and a detergent such as polyoxyl stearate mixed for form a stable cream. The active alcohols, e.g. one or more of 1-docosanol, 1-tetracosanol and 1-hexacosanol is added to the carrier in amounts from about 0.1 to about 25 percent by weight, typically in the range of from 1 to 5 percent. Higher concentrations of the active alcohol(s) may be used but no increase in efficacy results from concentrations above about 15 to 25 weight percent. The concentration of the active alcohol(s) is not critical, but optimum efficacy coupled with efficient use of the active ingredient would be found in the 1 to 5 weight percent range.

Another suitable composition for use in the method of this invention would be a cream formulated of water, white petrolatm, isopropyl myristate, lanolin alcohols, mineral oil and cetylstearyl alcohol into which from 1 to 5 percent of C-20 to C-26 alcohols, e.g. one or more alcohols selected from the group consisting of 1-docosanol, 1-tetracosanol and 1-hexacosanol has been intimately mixed.

An alternative suitable composition for use in this invention may be formulated of stearyl alcohol, petrolatum, water and mineral oil stabilized with a detergent such as sodium lauryl sulfate and may include a preservative such as methylparaben or propylparaben, and an effective amount, typically from about 0.1 to 5 percent by weight of one or more alcohols selected from the group consisting of 1-docosanol, 1-tetracosanol and 1-hexacosanol.

In all cases, suitale preservatives, such as ethylene diamine tetraacetate salts, methylparaben, propylparaben, etc., may be added to prevent bacterial and fungal growth. Penetrants, such as a zone, may also be added if desired.

The method of the present invention will require application to the inflamed area of skin or membrane of compositions, such as those described above as merely exemplary, in which the active ingredient consists essentially of one or more aliphatic alcohols having from 20 to 26 carbons in the aliphatic chain, an exemplary composition comprising one or more alcohols selected from the group consisting of 1-docosanol, 1-tetracosanol and 1-hexacosanol. Three to 6 appliccations of the ointment or ocream per day will, in most cases, be expected to produce prompt relief from the itching, discomfort associated with such diseases and promote healing of damaged tissues within a few days to a few weeks.

The method described is useful in treating a wide variety of viral and inflammatory diseases, examples of which include herpes, simplex, eczema, shingles psoriasis, atopic dermatitis, and in treating inflammation resulting from burns, lacerations and acute injuries.

It will be readily understood from the foregoing that the essential constituent(s) of the compositions useful in the present method is one or more aliphatic alcohols having from 20 to 26 carbons in the aliphatic chain of the alcohol(s), and that the composition of the carrier is non-critical and subject to great variation.

INDUSTRIAL APPLICATION

This invention is useful in treating virus-induced inflammatory diseases of humans and other animals, and inflammation resulting from burns, lacerations and acute injuries.

What is claimed is:

1. A method treating virus-induced and inflammatory diseases of skin and membranes in humans or animals, comprising topical application of a composition consisting of one or more of the aliphatic alcohols docosanol, tetracosanol and hexacosanol in a concentrration of from 0.1 to 25 percent by weight in a physiologically compatible carrier to the inflalmed skin or membrane of the patient to be treated.

2. The method of claim 1 wherein said alcohols are in a concentration of from about 1 to about 5 percent.

* * * * *

E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

MAINTENANCE FEE TRANSMITTAL FORM

Assistant Commissioner for Patents
ATTN: BOX M. FEE
Washington, D.C. 20231

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on

April 17, 1997
(Date)

Ned A. Israelsen, Reg. No. 29,655

Dear Sir:

Enclosed herewith is the payment of the maintenance fee for the listed patent.

(X) A check in the amount of $1,025 for the full payment of the maintenance fee and any necessary surcharge on the following patent is enclosed.

(X) The Commissioner is hereby authorized to charge any deficiency in the payment of the required fee or credit any overpayment to Deposit Account No. 11-1410. A duplicate copy of this transmittal is enclosed.

(X) Return prepaid postcard.

Patent No.	Fee Code	Maintenance Fee Amount	Surcharge Amount	U.S. App. No.	Patent Date	Application Filing Date	Payment Year	Small Entity?
4,874,794	284	$1,025	$0	07/345,084	10/17/89	04/28/89	08	Yes
TOTAL PAYMENT:			$1,025					

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4-17-97

By: _____
Ned A. Israelsen
Registration No. 29,655
Attorney of Record

NAI-1592:cd
041797

KNOBBE, MARTENS, OLSON & BEAR, LLP
620 NEWPORT CENTER DR 16TH FLOOR NEWPORT BEACH, CA 92660
(714) 760-0404 FAX (714) 760-9502

FILE COPY

LIDAK.024A

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	David H. Katz, M.D.
Patent No.	:	07/345,084
Issued	:	October 17, 1989
For	:	INFLAMMATORY DISEASE TREATMENT
Examiner	:	S. Friedman

Group Art Unit Unknown

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231 on

November 14, 1994
(Date of Deposit)

Ned A. Israelsen, Reg. No. 29,655
Name of applicant, assignee or Registered Representative

Signature

November 14, 1994
Date of Signature

TRANSMITTAL LETTER

Hon. Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Enclosed in the above-identified patent application are the following:

1. Revocation and Power of Attorney (2 pages);

2. A small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.

3. Return postcard.

Please charge our Deposit Account No. 11-1410 for any additional fees which may be required or credit our account for any overpayment. A copy of this letter is enclosed for this purpose.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR

Dated: 11-14-94

By: _____

Ned A. Israelsen
Registration No. 29,655
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(619) 235-8550

NAI-7631:CD
111194

LIDAK.024A

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	David H. Katz, M.D.
Serial No.	:	07/345,084
Issued Patent No.	:	4,874,794
Filed	:	April 28, 1989
For	:	INFLAMMATORY DISEASE TREATMENT
Examiner	:	S. Friedman

ESTABLISHMENT OF RIGHT OF ASSIGNEE TO TAKE ACTION
AND
REVOCATION AND POWER OF ATTORNEY

Hon. Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

The undersigned is empowered to act on behalf of the assignee indicated below (the "Assignee"). The assignment of this invention from the inventor(s) to the Assignee is recorded by the Patent and Trademark Office Assignment Branch at Reel 5293/Frame 0061. This Assignment represents the entire chain of title of this invention from the inventor(s) to the Assignee. I have reviewed this Assignment, and to the best of the Assignee's knowledge and belief, the Assignee is the owner of the entire right, title and interest in the above-referenced application.

I declare that all statements made herein are true, and that all statements made upon information and belief are believed to be true, and further, that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that willful, false statements may jeopardize the validity of the application, or any patent issuing thereon.

The undersigned hereby revokes any previous powers of attorney in the subject application, and hereby appoints Louis J. Knobbe, Registration No. 18,780; Don W. Martens, Registration No. 21,107; Gordon H. Olson, Registration No. 20,319; James B. Bear, Registration No. 25,221; Darrell L. Olson, Registration No. 28,247; William B. Bunker, Registration No. 29,365; William H. Nieman, Registration No. 30,201; Lowell Anderson, Registration No. 30,990; Arthur S. Rose, Registration No. 28,038; James F. Lesniak, Registration No. 25,240; Ned A. Israelsen, Registration No. 29,655; Drew S. Hamilton, Registration No. 29,801; Jerry T. Sewell,

Registration No. 31,567; John B. Sganga, Jr., Registration No. 31,302; Edward A. Schlatter, Registration No. 32,297; Gerard von Hoffmann, Registration No. 33,043; William C. Rooklidge, Registration No. 31,791; Joseph R. Re, Registration No. 31,291; John M. Carson, Registration No. 34,303; Andrew H. Simpson, Registration No. 31,469; Daniel E. Altman, Registration No. 34,115; Anita M. Kirkpatrick, Registration No. 32,617; Ernest A. Beutler, Registration No. 19,901; Vito A. Canuso, Registration No. 35,471; William H. Shreve, Registration No. 35,678; Stephen C. Jensen, Registration No. 35,556; Steven J. Nataupsky, Registration No. 37,688; Michael Fedrick, Registration No. 36,799; Michael H. Trenholm, Registration No. 37,743; AnneMarie Kaiser, Registration No. 37,649; Darryl A. Smith, Registration No. 37,723; Edward J. Treska, Registration No. 37,744; Nancy Ways Vensko, Registration No. 36,298; Jonathan A. Barney, Registration No. 34,292; John R. King, Registration No. 34,362; Richard C. Gilmore, Registration No. 37,335; Stephen S. Korniczky, Registration No. 34,853; Myra H. McCormack, Registration No. 36,602; Raimond J. Salenieks, Registration No. 37,924; Renée E. Canuso, Registration No. 36,657; Guy L. Cumberbatch, Registration No. 36,114; and Michael L. Fuller, Registration No. 36,516, Knobbe, Martens, Olson & Bear, 620 Newport Center Drive, Sixteenth Floor, Newport Beach, California 92660, Telephone (714) 760-0404, as its attorneys with full power of substitution and revocation to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected herewith. This appointment is to be to the exclusion of the inventor(s) and his attorney(s) in accordance with the provisions of 37 C.F.R. § 3.71.

Please direct all communications relative to said application to the following correspondence address:

Ned A. Israelsen
KNOBBE, MARTENS, OLSON & BEAR
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
Telephone: (619) 235-8550

Lidak Pharmaceuticals

Dated: 11-8-94

By: David H. Katz
David H. Katz, M.D.

Title: President

Address: 11077 North Torrey Pines Road
La Jolla, CA 92037

NAI-7603:cd
103194

PAYOR NUMBER
004993

GRANT L. HUBBARD
NELSON, HUBBARD & ROEDIGER
2623 NORTH SEVENTH STREET
PHOENIX, AZ 85006

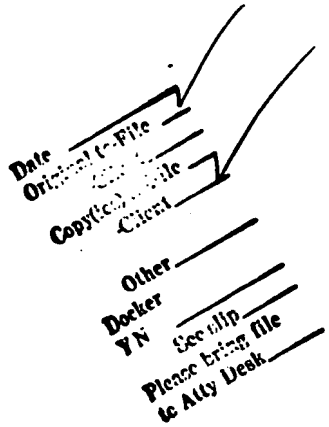
MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	STATUS
1	4,874,794	183	465	- -	07/345,084	10/17/89	04/28/89	PAID



If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

Attorney Docket LIDAK-024A

OMB Approved NO. 0651-001

FORM PTO-1536
(10-85)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

MAINTENANCE FEE TRANSMITTAL FORM

Address to: Commissioner of Patents and Trademarks
Box M. Fee
Washington, D.C. 20231

Enclosed herewith is the payment of the maintenance fee(s) for the listed patent(s).

1. ☒ A check for the amount of $ 465.00 for the full payment of the maintenance fee(s) and any necessary surcharge on the following patents is enclosed.
2. ☐ The Commissioner is hereby authorized to charge $ _____ to cover the payment of the fee(s) indicated below to Deposit Account No. _____.
3. ☒ The Commissioner is hereby authorized to charge any deficiency in the payment of the required fee(s) or credit any overpayment to Deposit Account No. 08-3102.

*Information required by 37 CFR 1.366(c)(columns 1 & 5). *Information requested under 37 CFR 1.366(d)* (columns 2-4 & 6-9)

Item	Patent Number* 1	Fee Code 2	Maintenance Fee Amount 3	Surcharge Amount 4	U.S. Serial Number* 5 [06/555/555]	Patent Date 6 mm/dd/yy	Application Filing Date 7 mm/dd/yy	Payment Year 8	Small Entity? 9
1	4,874,794	283	465.00	-0-	07/345,084	10/17/89	4/28/89	3.5	YES
2									
3									
4									
5									
6									
7									
8									
Sub-totals—Columns 3 & 4			465.00	-0-					
Total Payment			$465.00						

Use additional sheets for listing additional patents.

(For Office Accounting Use Only)

Attorney Docket LIDAK-024A

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent
Patent No. 4,874,794
Issue Date October 17, 1989

Application
Serial No. 07/ 345,084
Filing Date April 28, 1989

WARNING: Mandatory Identifiers: Maintenance fee (and surcharge, if any) payment must correctly identify: (1) the patent number (or reissue patent number, if a reissue) and (2) the serial number of the actual U.S. application (or reissue application) leading to issuance of that patent. 37 CFR 1.366(c) and (d).

(also complete the following additional information, if applicable)

The above-identified patent:

☐ is a reissue of original Patent No.: _____, original issue date _____; original application serial number 0 /_____, original filing date _____.

☐ resulted from the entry into the U.S. under 35 USC 371 of international application _____ filed on _____.

Box M. Fee
Commissioner of Patents and Trademarks
Washington, D.C. 20231

PAYMENT OF PATENT MAINTENANCE FEE (APPLICATION FILED ON OR AFTER AUGUST 27, 1982)

WARNING: While anyone may pay the maintenance fee on a patent (37 CFR 1.366), all PTO notices and correspondence will be mailed to the "fee address" set forth in 37 CFR 1.363. Notice of July 30, 1984 (1046 O.G. 23-37).

NOTE: The United States filing date of the application actually leading to the patent controls in original, in continuation, c-i-p, and divisional applications under 35 U.S.C. 120 and in applications claiming priority under 35 U.S.C. 119. 37 CFR 1.362(c)(1) to (3).

CERTIFICATION OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited on the date shown below with the United States Postal Service in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

(check and complete appropriate item below):

☒ 37 CFR 1.8(a) with sufficient postage as first class mail

or

☐ 37 CFR 1.10 as "Express Mail Post Office to Addressee" Mail Label No. _____

CYNTHIA HOLT
(Type or print name of person mailing paper)

Date October 30, 1992

Cynthia Holt
(Signature of person mailing paper)

NOTE: The filing date of ... original non-reissue controls as to whether a maintenance fee is due for a reissue patent. 37 CFR 1.362(b) and 37 CFR 1.362(c)(4).

NOTE: No maintenance fees are due for design or plant patents. 37 CFR 1.362(b).

1. Enclosed is the payment of the maintenance fee for this patent.

NOTE: Paragraph (e) of § 1.366 specifies that maintenance fee payments and any surcharges relating thereto must be submitted separate from any other payments for fees or charges or the payment will not be accepted.

2. MAINTENANCE FEE

WARNING: Any payment or authorization filed at any time other than that set forth in § 1.362(d), (e) or (f) for the fee itself, and surcharge, if any, (see below), will not serve as a payment of the maintenance fee, except insofar as a delayed payment of the maintenance fee is accepted by the Commissioner pursuant to § 1.378. A new authorization to charge a deposit account or other form of payment will have to be submitted at the approporiate time for each of the maintenance fees. Notice of July 30, 1984 (1046 O.G. 28-37) and 37 CFR 1.366(d).

NOTE: These fees are subject to adjustment in accordance with the provisions of Pub. L. 97-247 on October 1, 1985, and every third year thereafter, to reflect fluctuations occurring during the previous three years in the Consumer Price Index, as determined by the Secretary of Labor. If, the amount of the maintenance fee is correct on the date it is paid and credited to the patent, a later change in the maintenance fees to reflect changes in the Consumer Price Index will not require a modification in the amount paid. 37 CFR 1.366(b).

NOTE: 37 CFR 1.362(d) sets forth the time periods when maintenance fees can be paid without a surcharge. Those periods, referred to generally as the "window period" are the six month periods preceding each due date, i.e., 3 years through 3 years and six months, 7 years through 7 years and six months, and 11 years through 11 years and six months after grant of the patent. The "due dates" are defined in 35 U.S.C. 41(b). A maintenance fee paid on the last day of a window period can be paid without surcharge. The last day of a window period is the same date (anniversary date) the patent was granted 3 years and six months, 7 years and six months, or 11 years and six months after grant of the patent.

NOTE: 37 CFR 1.362(f) specifies that where the last day for paying a maintenance fee falls on a Saturday, Sunday or a federal holiday within the District of Columbia, the maintenance fee may be paid on th next succeeding day which is not a Saturday, Sunday, or federal holiday.

The fee payment is being made during the window period and is for the after grant period of:

	FEE	
	OTHER THAN SMALL ENTITY (Fee Code)	SMALL ENTITY (Fee Code)
[X] 3 1/2 years (37 CFR 1.20(h))	[ ]$ 930.00(183)	[X]$ 465.00(283)
[ ] 7 1/2 years (37 CFR 1.20(i))	[ ]$1,870.00(184)	[ ]$ 935.00(284)
[ ] 11 1/2 years (37 CFR 1.20(j))	[ ]$2,820.00(185)	[ ]$1,410.00(285)
	Fee due 465.00	

3. SURCHARGE—37 CFR 1.20(l)

NOTE: 37 CFR 1.362(e) sets forth time peiods when maintenance fees can be paid with a surcharge, i.e., 3 years and 6 months and through the day of the 4th anniversary, 7 years and 6 months and through the

(check and complete the following, if applicable)

☐ This payment is being made during the surcharge period and the additional fee due is also being paid.

☐ small entity $60.00—Fee Code 277

☐ other than small entity $120.00—Fee Code 177

Surcharge fee due -0-

TOTAL FEE BEING PAID 465.00

(complete 4 or 5 below, if applicable)

4. SMALL ENTITY

☐ Attached herewith is a verified statement establishing small entity status.

☒ A verified statement establishing small entity status for this patent was filed on April 28, 1989 (*date of filing verified statement*).

☒ and it is confirmed that small entity status for this patent has been checked and is still in effect.

5. LOSS OF ENTITLEMENT TO SMALL ENTITY STATUS

NOTE: 37 CFR 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in . . . patent prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate pursuant to § 1.19 of this Part." From the wording of 37 CFR 1.28(a): notification of change of status (a) must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity. See also 37 CFR 1.366(f).

Also, communications related to maintenance fee payments, e.g., loss of small entity status, should be addressed additionally marked "Box M. Fee" 37 CFR 1.1(d).

☐ The status of this patent has changed from that of small entity to other than that of small entity.

6. FEE PAYMENT

NOTE: The maintenance fee and any necessary surcharge may be paid in the manner set forth in § 1.23, i.e., it should be in United States specie, Treasury notes, national bank notes, post office money orders, or by certified check. As indicated in § 1.23, if the maintenance fee payment is sent in any other form, the Office may delay or cancel the credit until collection is made. For example, a personal or other uncertified check drawn on a United States bank which is not immediately negotiable, e.g., because of lack of signature or insufficient funds, will not constitute payment of a maintenance fee. However, a personal check drawn on a United States bank can be used if it is immediately negotiable. Any remittance from foreign countries must be payable and immediately negotiable in the United States for the full amount of the maintenance fee required. Notice of July 30, 1984 (1046 O.G. 28-37).

NOTE: A maintenance fee payment, with or without surcharge, made during the window period does not require adjustment if the maintenance fees are thereafter increased to reflect increases in the Consumer Price Index. 37 CFR 1.366.

NOTE: An authorization is required to authorize the immediate charging of the fee to the deposit account and is improper if it only authorized the fee to be charged at a later date, e.g. on the last possible day of payment without surcharge. Any payment which fails to result in the entire proper amount of the maintenance fee being present on the due date will not constitute payment of the maintenance fee. Notice of July 30, 1984. 1046 O.G. 28-37.

☒ Enclosed is a check for the sum of $ 465.00.

☐ Please charge Account No. _____ the sum of $_____. A duplicate of this payment is attached.

7. AUTHORIZATION TO CHARGE ANY FEE DEFICIENCY

*WARNING: Since 37 CFR 1.366(b) specifies that a payment of less than the required amount (of maintenance fee and any required surcharge) will not constitute payment of a maintenance fee it would be the better practice to always check and complete this authorization to charge any fee deficiency. This practice will also guard against a holding of a failure to pay because of an unsigned or missing check or a check for an improper amount. **ORIGINAL SIGNATURE REQUIRED BELOW FOR DEPOSIT ACCOUNT TO BE CHARGED.***

☒ The Commissioner is hereby authorized to charge any maintenance and/or surcharge fee deficiency which may be due on this patent to Account No. 08-3102.

8. OVERPAYMENT

As to any overpayment made please

☒ Credit to Account No. 08-3102

☐ Send refund check.

Reg. No. 24,193

SIGNATURE OF ATTORNEY

GRANT L. HUBBARD

Type or print name of attorney

Tel. No. (602) 263-8782

2623 North Seventh Street

P.O. Address

PAYOR NO. _____

Phoenix, Arizona 85006

Attorney Docket LIDAK-024A

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent		**Application**	
Patent No.	4,874,794	Serial No. 0 7/	345,084
Issue Date	October 17, 1989	Filing Date	April 28, 1989

WARNING: ***Mandatory Identifiers:*** *Maintenance fee (and surcharge, if any) payment must correctly identify: (1) the patent number (or reissue patent number, if a reissue) and (2) the serial number of the actual U.S. application (or reissue application) leading to issuance of that patent. 37 CFR 1.366(c) and (d).*

(also complete the following additional information, if applicable)

The above-identified patent:

☐ is a reissue of original Patent No.: _____, original issue date _____; original application serial number 0 /_____, original filing date _____

☐ resulted from the entry into the U.S. under 35 USC 371 of international application _____ filed on _____.

Box M. Fee
Commissioner of Patents and Trademarks
Washington, D.C. 20231

FEE ADDRESSEE FOR RECEIPT OF PTO NOTICES RELATING TO MAINTENANCE FEES

1. This letter is to specify that the FEE ADDRESSEE for this patent is (*set forth name and mailing address of the fee addressee*):

Grant L. Hubbard
NELSON, HUBBARD & ROEDIGER
2623 North Seventh Street
Phoenix, Arizona 85006

2. Any prior FEE ADDRESSEE for this patent is hereby revoked.

3. It is certified that the person whose signature appears below has the authority to change the FEE ADDRESSEE for this patent.

Date October 30, 1992.

GRANT L. HUBBARD
Type or print name of person signing

2623 N Seventh Street
P.O. Address
Phoenix, AZ 85006

Identity of signatory:

- ☐ Inventor (patentee)
- ☐ Assignee of complete interest
- ☐ Person authorized to sign on behalf of assignee
- ☒ Attorney or agent of record

Tel. No. (602) 263-8782
Reg. No. 24,193

(complete the following if applicable)

Type name of Assignee

Address of Assignee

Title of person authorized to sign on behalf of assignee

Assignment recorded in PTO on _____ Reel _____ Frame _____

(complete the following, if applicable)

PAYOR NUMBER _____

F

AVANIR.000GEN

EXHIBIT F

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of :		KATZ, David H.	Group Art Unit 125
Appl. No.	:	07/345,084	
Filed	:	April 28, 1989	
Patent No.	:	U. S. Patent No. 4,874,794	
Issued	:	October 17, 1989	
For	:	INFLAMMATORY DISEASE TREATMENT	
Examiner	:	FRIEDMAN, Stanley J.	

Assistant Commissioner for Patents
Washington, D.C. 20231
Box Patent Ext.

DECLARATION UNDER 37 C.F.R. §1.740(b) FOR EXTENSION OF PATENT TERM

I Mark R. Benedict, patent attorney with the firm of Knobbe, Martens, Olson & Bear, LLP, and registered to practice before the Patent and Trademark Office, have Power of Attorney to act on behalf of the assignee, AVANIR Pharmaceuticals, the owner of the entire right, title and interest in U. S. Patent No. 4,874,794, in executing this Declaration and the attached application for extension of patent term.

I hereby declare the following:

(1) I have reviewed and understand the contents of the application being submitted pursuant to 37 C.F.R. §1.740;

(2) I believe the patent is subject to extension pursuant to §1.710;

(3) I believe an extension of the length claimed is justified under 35 U.S.C. §156 and the applicable regulations; and

(4) I believe the patent for which extension is sought meets the conditions for extension of the term of a patent as set forth in §1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 9/22/00

Mark R. Benedict
Registration No. 44,531
Attorney of Record

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of :		KATZ, David H.	Group Art Unit 125
Appl. No.	:	07/345,084	
Filed	:	April 28, 1989	
Patent No.	:	U. S. Patent No. 4,874,794	
Issued	:	October 17, 1989	
For	:	INFLAMMATORY DISEASE TREATMENT	
Examiner	:	FRIEDMAN, Stanley J.	

Assistant Commissioner for Patents
Washington, D.C. 20231
Box Patent Ext.

CERTIFICATION

The undersigned hereby certifies that the attached photocopy is an exact duplicate of the application for extension of the term of U. S. Patent No. 4,874,794 under 35 U.S.C. 156, including its attachments and supporting papers, mailed to the U. S. Patent and Trademark Office herewith on this date.

Date: 9/22/00

Mark R. Benedict
Registration No. 44,531
Attorney of Record

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